



## Complete Summary

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### GUIDELINE TITLE

Use of bisphosphonates in women with breast cancer.

### BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Use of bisphosphonates in patients with breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Dec [online update]. 23 p. (Practice guideline; no. 1-11). [59 references]

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## SCOPE

### DISEASE/CONDITION(S)

Breast cancer with bone metastases

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness

Prevention

Treatment

### CLINICAL SPECIALTY

Internal Medicine

Oncology

Radiation Oncology

### INTENDED USERS

Physicians

## GUIDELINE OBJECTIVE(S)

To make recommendations regarding the use of bisphosphonates in patients with breast cancer:

- To reduce pain, reduce the likelihood of skeletal events other than hypercalcemia, improve quality of life, or improve survival in women with bone metastases due to breast cancer
- To reduce the likelihood of bone metastases or improve survival in women with breast cancer that is locally advanced or metastatic to sites other than bone
- To reduce the risk of bone metastases or to improve survival in women with early stage breast cancer

## TARGET POPULATION

Women with breast cancer

## INTERVENTIONS AND PRACTICES CONSIDERED

Bisphosphonates (clodronate, pamidronate, ibandronate, or zoledronate)

## MAJOR OUTCOMES CONSIDERED

- Bone pain
- Skeletal events other than hypercalcemia
- Quality of life
- Adverse effects
- Development of bone metastases
- Survival

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Medline database was searched from 1976 to August 2002 using disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s]), treatment-specific terms (diphosphonates, bisphosphonates, clodronate, pamidronate, etidronate, alendronate, ibandronate, zoledronate), and design-specific terms (meta-analysis, randomized controlled trial[s], practice guideline). The searches were not restricted by language. Issue 3 (2002) of the Cochrane Library, the Physician Data Query (PDQ®) database ([http://www.cancer.gov/search/clinical\\_trials/](http://www.cancer.gov/search/clinical_trials/)), conference proceedings from the American Society of Clinical Oncology (ASCO) (1997-2002) and the San Antonio

Breast Cancer Symposium (2001), and bibliographies were also searched. The Canadian Medical Association (CMA) Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), the National Guideline Clearinghouse (<http://www.guideline.gov/>) and other web sites were searched for existing evidence-based practice guidelines.

#### Inclusion Criteria

Articles were eligible if they met all of the following criteria:

1. They were published reports, or abstracts from the American Society of Clinical Oncology or San Antonio Breast Cancer meetings.
2. They presented results of a meta-analysis or randomized controlled trial that compared:
  - i. treatment with a bisphosphonate to observation or placebo,
  - ii. two bisphosphonates,
  - iii. two or more doses of the same bisphosphonate, or
  - iv. the same bisphosphonate given by two routes of administration.
3. Trial participants were primarily patients with breast cancer (early-stage or advanced), although trial participants could also include patients with other solid tumours or myeloma.
4. Results were reported, by treatment group, for at least one of the following outcomes: survival, quality of life, and adverse effects. Additional outcomes of interest for patients with bone metastases from breast cancer included bone pain (measured using a pain scale or analgesic consumption) and skeletal events, other than hypercalcemia (as bisphosphonates are acknowledged to be an effective intervention for this complication). The development of bone metastases was also an outcome of interest in patients without bone metastases at the time of randomization.

Evidence-based practice guidelines and systematic reviews addressing the guideline questions were also included.

#### NUMBER OF SOURCE DOCUMENTS

The literature search found three evidence-based practice guidelines, two systematic reviews, and twenty-eight randomized trials.

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

#### METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials  
Review of Published Meta-Analyses  
Systematic Review

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Because a well-conducted published meta-analysis was available, the Breast Cancer Disease Site Group (DSG) did not conduct their own pooled analysis. The DSG did, however, conduct supplementary sensitivity analyses to make the meta-analysis more directly relevant to the guideline questions listed in the original guideline document and to assess the impact of recently published evidence. For both the published meta-analyses and the sensitivity analyses by the DSG, the overall effect of bisphosphonates versus control was determined by pooling data using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). Results are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI). A relative risk (RR) >1.0 indicates that patients in the bisphosphonate group had a higher probability of experiencing an event compared with those in the control group; conversely, a relative risk <1.0 favours bisphosphonate over control. The published meta-analysis presented pooled results based on the fixed-effects model but noted that "random-effects models were also examined". In order to facilitate direct comparisons with the results of the published meta-analysis, the DSG used the fixed-effects model for sensitivity analyses.

In the published meta-analysis, mortality data were pooled across a set of trials in patients with advanced breast cancer. In the first sensitivity analysis, the DSG restricted this analysis to patients with bone metastases. The second sensitivity analysis was restricted to patients without evidence of bone metastases. In the third sensitivity analysis, mortality data from a trial of adjuvant bisphosphonates that was published after completion of the published meta-analysis was added. In all cases, the numbers of patients dying during the trial and the numbers randomized were used for the meta-analysis.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In 2002, the Breast Cancer Disease Site Group (DSG) reviewed the updated and rewritten guideline report, which incorporated new evidence on the long-term use of oral clodronate and on adjuvant bisphosphonates, as well as data from two trials comparing zoledronate to pamidronate. The scope of the revised guideline was similar to the original but the single guideline question "Should bisphosphonates be used in patients with bone metastases from breast cancer?" was expanded to three: one related to patients with bone metastases, one to patients with advanced disease but no bone metastases, and one to the adjuvant use of bisphosphonates. The DSG suggested that the questions be further modified to include the outcomes of interest in each of these three settings. They also identified a need for more discussion on gastrointestinal toxicity and any new evidence presented at the 2002 American Society of Clinical Oncology (ASCO) meeting.

The DSG noted that it is uncertain whether bisphosphonate therapy can prevent skeletal complications in patients with a short life expectancy (less than 4 to 6

months), because the largest studies excluded these patients. Although the median time to first skeletal event was shorter than six months in the pamidronate studies that provide the best available evidence, the data do not show a difference emerging between pamidronate and control until approximately six months after study entry. The data suggest that the use of bisphosphonates to prevent skeletal events will require a considerable duration of administration. In contrast, pain relief can occur within days when bisphosphonates are used as an adjunct for pain control. Ultimately, the decision about whether or not it is appropriate to offer therapy when survival may be short rests with the treating physician.

DSG members discussed the use of clodronate in patients who have difficulty tolerating oral medications because of existing nausea, vomiting or esophagitis. The DSG strongly advocated that such patients should be spared a trial of oral clodronate before being offered intravenous pamidronate. Two DSG members suggested extending this recommendation to patients without nausea or vomiting, but in whom there is a high likelihood of gastrointestinal upset related to any medication, as well as patients who are likely to develop nausea, vomiting or esophagitis from planned radiotherapy or emetogenic medication. Other DSG members felt that predicting which patients may develop these problems would be difficult and that they could be managed by a brief interruption of oral clodronate or by switching to intravenous pamidronate at the next cycle of chemotherapy.

The DSG agreed that the revised guideline should include four new recommendations, in addition to those made in 1998:

1. Patients with a short expected survival (i.e., less than 6 months) who have well controlled bone pain may be an exception to the recommendation for bisphosphonates in women with bone metastases from breast cancer.
2. Patients with bone metastases from breast cancer who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate, without a trial of oral clodronate.
3. Intravenous zoledronate is an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
4. Bisphosphonates are not recommended to prevent bone metastases in women with locally advanced breast cancer or non-skeletal metastases.

The DSG considered extending their recommendations to men with breast cancer. No randomized trials have assessed the efficacy of bisphosphonates in men with breast cancer, but men have participated in randomized trials of bisphosphonates for multiple myeloma. Since there is no evidence to suggest that the benefit in multiple myeloma is gender specific, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone. The DSG also noted that there was no evidence for continuing or switching bisphosphonates after a skeletal event. Qualifying statements were added to the recommendations to address these two issues.

#### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

#### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 127 practitioners in Ontario (88 Medical Oncologists and 39 Radiation Oncologists). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGIP) report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee for review and approval. Seven members of the Practice Guidelines Coordinating Committee returned ballots. All seven Practice Guideline Coordinating Committee members approved the practice guideline report as written. One member approved the guideline and provided suggestions for consideration by the Breast Cancer Disease Site Group.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Breast Cancer Disease Site Group and the Practice Guidelines Coordinating Committee.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

- Women with breast cancer who have bone metastases should be offered treatment with oral clodronate or intravenous pamidronate.
  - An exception may be patients with a short expected survival (i.e., less than six months), who have well controlled bone pain.
  - Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate.
  - Intravenous zoledronate is an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
  - Intravenous clodronate has not been examined for its ability to reduce morbidity from bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.

- In patients with bone metastases and pain, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control.
- Bisphosphonates are not recommended to prevent bone metastases or improve survival in women with locally advanced breast cancer or non-skeletal metastases.
- Current evidence is insufficient to support the use of bisphosphonates as adjuvant therapy to either prevent skeletal events or improve survival in women with early-stage breast cancer.

## CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The literature search found the following articles and abstracts, which are summarized in the practice-guideline report:

- three evidence-based practice guidelines from other guideline-development groups that provide recommendations on the use of bisphosphonates in breast cancer;
- two systematic reviews: one without meta-analysis, published in 1998, and one with meta-analysis, published in 2001;
- twenty-eight randomized trials, nine of which were not included in the most recent systematic review. Twenty-nine randomized trials were found by the literature search, but one cross-over trial of pamidronate versus placebo in ten patients was not included because of inadequate presentation of results.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Sixteen randomized trials evaluated the addition of oral or intravenous bisphosphonates to chemotherapy or hormonal therapy for women with bone metastases from breast cancer. Clodronate (eight trials), pamidronate (six trials) or ibandronate (two trials) were compared to placebo or no-treatment control. A published meta-analysis of published data from six trials detected a reduction in the risk of skeletal events (excluding hypercalcemia) with bisphosphonates (relative risk of skeletal event, 0.88; 95% confidence interval, 0.81 to 0.96;  $p=0.004$ ). Seven of nine double-blind trials and two of three open-label trials that assessed pain or analgesic use detected significantly reduced pain scores or analgesic use with bisphosphonates. Although five trials (four double-blind and one open-label) evaluated quality of life, there is no clear evidence of improvement with bisphosphonate therapy.
- Two randomized trials did not detect significant differences in skeletal events or pain between intravenous zoledronate and intravenous pamidronate in women with bone metastases from breast cancer.

- Three randomized trials evaluated the addition of oral bisphosphonates to chemotherapy or hormonal therapy for women with advanced breast cancer but no evidence of bone metastases. A published meta-analysis did not detect a significant difference in the risk of developing bone metastases (relative risk, 0.99; 95% confidence interval, 0.67 to 1.47) with bisphosphonates, compared to placebo or no treatment. Quality of life was measured in one trial, which did not detect a significant difference between pamidronate and control.
- A published meta-analysis of published data from nine trials did not detect a significant improvement in survival when bisphosphonates were administered to women with advanced breast cancer, with or without bone metastases (relative risk of death, 0.99; 95% confidence interval, 0.93 to 1.04).
- Three trials compared oral clodronate with placebo or no treatment as adjuvant therapy for early-stage breast cancer. They obtained conflicting results with respect to the effect of bisphosphonates on the development of bone metastases and survival.

## POTENTIAL HARMS

- One randomized placebo-controlled trial detected an increased rate of gastrointestinal complaints with oral clodronate. Local reactions at the injection site were more common with pamidronate than with placebo, no-treatment control, or zoledronate. Uveitis is a rare but documented complication of treatment with pamidronate, requiring urgent referral to an ophthalmologist.
- The standard doses of the bisphosphonates reviewed here are: oral clodronate 1.6 g/day, intravenous pamidronate 90 mg every 3-4 weeks, and intravenous zoledronate 4 mg every 3-4 weeks. Randomized trials that compared different doses detected no significant differences in pain scores among doses, but observed that 3.2 g of clodronate was associated with hypocalcemia and that pain was reduced more quickly with 90 mg of pamidronate compared to lower doses.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- There is no evidence from clinical trials that address the optimal duration of bisphosphonate use.
- There are no data on the efficacy of bisphosphonates in men with breast cancer, but men have participated in randomized trials of bisphosphonates for multiple myeloma. Since there is no evidence to suggest that the benefit detected in multiple myeloma trials is gender specific, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.



## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Use of bisphosphonates in patients with breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Dec [online update]. 23 p. (Practice guideline; no. 1-11). [59 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

1998 Nov 9 (revised Dec 2002)

### GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health.

### SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

### GUIDELINE COMMITTEE

Provincial Breast Cancer Disease Site Group

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Breast Cancer Disease Site Group disclosed potential conflict of interest information.

## GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

## GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Use of bisphosphonates in patients with bone metastases from breast cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This summary was updated by ECRI on April 12, 2002 and most recently on July 21, 2003. The most recent information was verified by the guideline developer as of August 6, 2003.

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